REMARKS

Favorable consideration and allowance are respectfully requested for claims 1-5 in view of the following remarks.

The Examiner's withdrawal of the rejections under 35 U.S.C. § 102 is acknowledged with appreciation. The remaining rejections of claims 1-5 under 35 U.S.C. § 103 as obvious over either Lepran *et al.* or WO 97/46241 (the '241 application) are respectfully traversed.

Reviewing the Office Action mailed March 18, 2004, it appears there is either a significant misconception of the present invention or of the difference between damage to heart tissue incurred subsequent to myocardial infarction, on one hand, and the relevance of disclosures related to arrhythmias (Lepran) or the treatment of congestive heart failure (the '241 application).

Cardiovascular and, in particular, heart conditions are very complex, and it is never evident to a person of ordinary skill in the art whether a compound found to be suitable for treating one cardiovascular condition might be suitable for treating another condition. The Office Action asserts that one of skill in the art would believe that methods for treating arrhythmias (Lepran) or for treating congestive heart failure (the '241 application) would also be suitable for inhibiting tissue damage after a myocardial infarction. The present record, however, provides no linkage between either arrhythmias or congestive heart failure and inhibiting tissue damage after a myocardial infarction. In fact, the declaration of Professor Dr. Rupp clearly refutes the existence of any relation between the subject matter of the cited references and that of the presently-claimed invention.

The Office Action indicates that Lepran and the '241 application do not state "post myocardial management or recovery or rehabilitation" or "post myocardial infarction or recovery of myocardial status." Not only is there no explicit suggestion

of a treatment for tissue damage following myocardial infarction, there is also no implict suggestion of such a treatment.

Obviousness is determined by resolving whether a person of ordinary skill in the relevant art, reviewing the cited references, would find some motivation, either in the references themselves or in the knowledge of that person of ordinary skill, first, to even consider the references applicable to the matter at hand and second, to try to modify or otherwise combine the references. In the present instance, a person of ordinary skill in the art would have no reason to consider the references relevant to postmyocardial infarction treatments. As explained in the previously-submitted responses and the declaration of Professor Dr. Rupp, the cited references provide no teaching relevant to inhibiting tissue damage by administering moxonidine after myocardial infarction. The treatments discussed in the references, one for arrhythmia and one for congestive heart failure, are separate and distinct from the claimed postmyocardial treatment and there is no reason to believe that a treatment for one would be successful or even useful as a treatment for the other.

The Lepran article relates to a method where moxonidine is applied before myocardial infarction to avoid arrhythmia. The claimed invention is directed to a method of inhibiting tissue damage following myocardial infarction. The Office Action improperly equates the term "damage" with "arrhythmias" or "ventricular fibrillation". See the last paragraph of the Office Action on page 3, stating that Lepran aims at arrhythmias occurring after myocardial infarction. Simply put, an arrhythmia is not the same as tissue damage. An arrhythmia is a cardiac dysfunction, that is, the heart muscle is not contracting with its normal rhythm. This dysfunctional condition does not amount to and is not at all the same as structural damage of the heart tissue, as is claimed. There is nothing in the record that explains why a person of ordinary skill in the art would believe the arrhythmia treatment taught in the Lepran article would have any bearing on inhibiting tissue damage following myocardial infarction. Arrhythmias may occur after myocardial

infarction, but in such a case, the arrhythmia is merely an event or condition following myocardial infarction and is not the same as "myocardial damage."

The Office Action asserts that the Lepran reference teaches that moxonidine decreases the infarct size of the heart in rats. However, these results are only applicable to moxonidine treatment before the coronary ligation. Further, close examination of the experimental results reveals that only the moxonidine pretreatment at a dosage of 0.03 mg/kg was effective to reduce infarct size. Pretreatment with a higher dosage of 0.10 mg/kg and pretreatment with a lower dosage of 0.01 mg/kg both resulted in "no significant change" of the infarct size. See page S11, column 2. Thus, only the middle of the three pretreatment dosages had a significant effect on tissue damage. This discrepancy is highly significant because it suggests either that if moxonidine is present during coronary ligation, it will likely not be effective to reduce infarction, or that the experimental data is unreliable.

Further discrepancies appear for the data relating to experiments on moxonidine pretreatment and survival rates during reperfusion after 6 minutes of myocardial ischemia. With a pretreatment dosage of 0.01 mg/kg, survival rates were reduced. Survival rates increased, however, with higher dosages of 0.03 and 0.10 mg/kg. See Table 3 on page S12. The authors provided no explanation for this decrease in the survival rate.

Taken together, these results show that the effects of pretreatment with moxonidine are unpredictable. The results related to the pretreatment effect of moxonidine on infarction provide no clear indication that moxonidine reduces infarction. According to the authors, at two out of three selected dosages, the results were insignificant. These scattered results would actually discourage one of skill in the art from trying to use moxonidine generally. Such a person would be more inclined to select another drug with better experimental data and greater relevance to inhibiting tissue damage. Of particular relevance here is the survival rate reduction caused by pretreatment of 0.01 mg/kg moxonidine after 6 minutes of myocardial ischemia. This reduction in survival rate would discount any positive

effects of the treatment and might even cause one to avoid trying to use moxonidine for cardiac events generally. As a result, this part of the Lepran article actually teaches away from using moxonidine.

Contrary to the Office Action, there is nothing implicit in the teachings of Lepran about post-myocardial infarction administration of moxonodine. Rather, the teachings, questionable as they are given the experimental results, are clearly limited to the administration of moxonidine before myocardial ischemia or myocardial infarction. The article itself states that "[o]ur model of short-term myocardial ischemia is not useful to study the entire sequence of ischemia-induced arrhythmias." See page S12, column 2. Thus, the authors of the Lepran article themselves expressly acknowledge that their methods are not applicable to all forms of ischemia-induced arrhythmias. Extending the arrhythmia treatment methods of the Lepran article to methods of avoiding tissue damage through administration after myocardial infarction ignores not only the lack of any linkage between arrythmias and postmyocardial infarction tissue damage, but also the limitations of the research expressly acknowledged by the authors of the article.

The author's ultimate conclusion is that moxonidine reduces the incidence of arrhythmias during the acute phase of experimental myocardial infarction. This has no bearing on or relevance to the effects of moxonidine to inhibit tissue damage, much less the inhibition of tissue damage following myocardial infarction. In all of the experiments discussed in the Lepran article, moxonidine was administered before the coronary ligation. Any treatment effective during the acute phase of an evolving myocardial infarction must be administered before that myocardial infarction and is effective because of its operation during that myocardial infarction. One of ordinary skill in the art would conclude that the action of moxonidine occurred during the coronary ligatiion induced myocardial ishemia. There was simply no discussion or teaching that moxonidine might be of any benefit if administered after myocardial infarction. Accordingly, Lepran's treatment to correct an irregular heart rhythm is of no relevance to treatments to avoid tissue damage

following myocardial infarction. The record lacks any explanation of why a person of ordinary skill in the art would have reason to believe that a treatment to improve an irregular heart rhythm would be at all effective to prevent heart tissue damage following myocardial infarction. For this reason, a person of ordinary skill in the art cannot be motivated by Lepran to select moxonidine to inhibit myocardial damage secondary to myocardial infarction.

The '241 application relates to the use of moxonidine to treat congestive heart failure. The notion that a treatment to inhibit tissue damage following myocardial infarction would be obvious in view of a treatment for congestive heart failure because congestive heart failure may occur after myocardial infarction is entirely without merit. There is no linkage between congestive heart failure and damage subsequent to myocardial infarction. The evidence of record supports the conclusion that there is no such linkage.

The expert declaration of Professor Dr. Rupp clearly describes the medical distinctness of congestive heart failure and myocardial infarction or related treatments. Congestive heart failure relates to the weak or diminished function of the heart, i.e., the heart muscle is unable to provide the powerful output required for proper blood circulation. In severe form, congestive heart failure may lead to pulmonary edema, where the imbalance in heart pump function causes an increase in lung fluid from pulmonary capillary leakage into the interstitium and alveoli of the lung. Congestive heart failure may be caused by any of a wide variety of mechanisms or conditions including vitamin deficiency, toxin exposure or genetic factors, among others. Treatments for congestive heart failure are aimed at improving the operation of the heart by causing the heart to operate more forcefully or efficiently. Typically this involves treating the underlying condition responsible for the heart's inadequate performance. Treatments for congestive heart failure may involve administration of angiotensin converting enzyme (ACE) inhibitors which reduce peripheral vascular resistance to allow increased bloodflow.

As explained in the declaration of Professor Dr. Rupp, the '241 application is limited to treatments for improving the operation of the heart through action on the hemodynamic parameters associated with congestive heart failure. In particular, the '241 application relates to the reduction of blood pressure in patients suffering from congestive heart disease. See the '241 application at pages 11 and 12. These treatments are entirely unrelated to, and have no bearing upon inhibiting tissue damage following myocardial infarction. The record provides no explanation of why a treatment to improve the function of the heart by reducing sympathetic activity would be expected to work to avoid tissue damage, much less to avoid tissue damage following myocardial infarction. Considering the declaration of Professor Dr. Rupp, which concludes that:

> [b]ecause the '241 application deals only with a treatment of congestive heart failure, and because treatments for congestive heart failure are only targeted at improving heart function, and cannot be assumed to be beneficial to inhibit damage secondary to myocardial infarction, the '241 application provides no teaching or suggestion to administer moxonidine to inhibit damage secondary to myocardial infarction.

the teachings of the '241 application are irrelevant to the present application.

The present invention is not directed to treating a particular cardiovascular event, nor is it directed to treating arrhythmias or congestive heart failure. Instead, the invention provides, for the first time, the unique and outstanding finding that moxonidine can preserve ischemic myocardium and inhibit necrosis. This is completely different from the centrally-mediated effects of moxonidine in relation to the hemodynamic functioning of the heart, as is addressed by the '241 application.

The post-myocardial infarction treatment of the present invention is provided in order minimize the risk of further destruction of heart tissue, which, if it were allowed to occur, would further impair the heart function. This is significantly different from the reasons for the treatments in the cited references, as explained above. Arrhythmia patients and congestive heart failure patients are distinct from

the patients of the present invention because there is no necessary connection between arrhythmia or congestive heart failure and avoiding further tissue damage in a patient who has suffered from myocardial infarction. Accordingly, a person of skill in the art would have no motivation to try to inhibit the destruction of heart tissue using the arrhythmia treatment methods of the Lepran article or the congestive heart failure methods of the '241 application.

As set forth in the Manual of Patent Examining Procedure (MPEP) a *prima facie* case of obviousness requires that three basic criteria be met: (i) a teaching or suggestion to one of ordinary skill in the art to modify a reference; (ii) a reasonable expectation of success; and (iii) the prior art must teach or suggest all the application's claim limitations. See the Manual of Patent Examining Procedures, § 706.02(j) (8th ed. August, 2001), Patent and Trademark Office, U.S. Department of Commerce.

In the present instance, there is no suggestion to one of ordinary skill in the art to modify the teachings of either Lepran or the '241 application so as to meet the limitations of the presently-pending claims. Moreover, the proposed modification requires one to disregard the teachings of the reference, as they relate to treatments for arrhythmias (Lepran) or the treatment of congestive heart failure (the '241 application). Given these teachings, one of skill in the art would have no reason to believe that administration of moxonidine would be of any benefit in inhibiting tissue damage following myocardial infarction. For this reason, there would not be any reasonable expectation of successful for such a modification. There is nothing in either of the references that even suggests that the administration of moxonidine after myocardial infarction would be at all beneficial to inhibit tissue damage. Accordingly, the references would not be considered helpful to a person of skill in the art trying to determine suitable treatments for postmyocardial infarction patients.

Without some suggestion or other incentive to believe that the administration of moxonidine would be beneficial to inhibit damage following myocardial infarction, it defies reason to state that one of skill in the art, having reviewed either of the

references, would find any motivation to try to modify the reference to arrive at the presently-claimed invention. As discussed in the Manual of Patent Examining Procedure, § 2144.08, at page 2100-138, (8th ed. August, 2001), the Federal Circuit has explained that "[A] proper analysis under § 103 requires, *inter alia*, consideration of . . . whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed compound or device, or carry out the claimed process." See *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Nothing in the cited references provides any type of motivation to carry out the claimed process. Thus, the claim rejections under § 103 cannot be properly maintained.

As explained above, there is no linkage between treatments to inhibit tissue damage following myocardial infarction and treatments to prevent arrhythmia or treatments for congestive heart failure. The present record provides no explanation of any such linkage. Not only is there no positive explanation of such a linkage in the record, the record includes detailed testimony from an expert in the field of cardiovascular diseases of how these conditions or events are different and why there is no linkage between the cited references and the presently-claimed method. Professor Dr. Rupp is an independent medical university professor with significant and highly relevant expertise in the field of cardiovascular diseases. As explained in his declaration, Professor Dr. Rupp quite clearly and unequivocally concludes that the cited references do not provide any suggestion or motivation to one of skill in the art to try to inhibit tissue damage by administering moxonidine after myocardial infarction. See paragraph 18 on page 7 of Dr. Rupp's declaration.

In view thereof, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) over Lepran and the '241 application are respectfully requested.

Conclusion

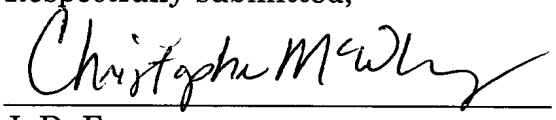
In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

Although a Petition for Extension of Time is submitted herewith, if necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response. Please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Attorney Docket No. 029300.50194US).

Respectfully submitted,

September 20, 2004



J. D. Evans
Registration No. 26,269

Christopher T. McWhinney
Registration No. 42,875

CROWELL & MORING LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844
JDE:CTM:tlm (029300.50194US; 338122)